PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1254PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/ES2003/000510	International filing date *(day/month/year)* 08.10.2003	Priority date *(day/month/year)* 08.10.2003
International Patent Classification (IPC) or both national classification and IPC C07C65/05		
Applicant INNOVAPROTEAN, S.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.03.2005	09.08.2005
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heibl, C Telephone No. +49 89 2399-8331

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/ES2003/000510

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 filed with telefax on 21.03.2005

Claims, Numbers

1-9 filed with telefax on 21.03.2005

Drawings, Sheets

1/1 filed with telefax on 21.03.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 - WO-A 98/46234
D2 - EP-A 082 404
D3 - WO-A 98/20864

The present invention provides 'diflunisal' derivatives having use as inhibitors of the formation of amyloid fibrils associated with transthyretin (amyloidogenesis inhibitors), thus being suitable for the treatment of neurogenerative diseases.

The present compounds of formula (I) (see claim 1) are in particular characterized by having a **iodine** substituent in **5**-position of the basic molecule (2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid). Since none of the prior art documents D1-D3 discloses such **5-iodo** derivatives, the claimed compounds (claims 1-3) and the subject-matter of claims 4-9 related herewith can be considered novel (Art. 33(2) PCT).

The effect of said iodation leading to an enhanced activity (amyloidogenesis inhibition) as compared to non-iodated derivatives (see the experimental part of the present application) cannot be derived from the teaching of the available prior art documents. Indeed, D1 which merely theoretically covers iodo derivatives of certain diflunisal ester derivatives (see the definition of R_3 which includes inter alia "halo" , the position of R_3 being not defined) relates to compounds having anti-platelet activity, hydroxy radical scavenging properties which makes them suitable for the treatment or control of thrombosis and ischaemic/perfusion injury of tissues such as liver.
D2 deals with analgesic and anti-inflammatory diflunisal derivatives, D3 with anti-inflammatory diflunisal derivatives which are also suitable for the treatment of neurogenerative diseases. In addition, neither D2 nor D3 suggests iodination of diflunisal derivatives.
Having regard to the prior art, the subject-matter of claims 1-9 is also considered to meet the requirements of Art. 33(3) PCT.

The subject-matter of claims 1-9 also meets the criteria Art. 33(4) PCT (industrial

applicability).